Title: Improved Adherence to Tacrolimus Once-Daily Formulation in Renal Recipients: A Randomized Controlled Trial Using Electronic Monitoring

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List of abbreviations used:

ADMIRAD: ADherence Measurement In stable Renal transplant patients following conversion from Prograft® to ADvagraf®

BID, twice-daily

BPAR, biopsy-proven acute rejection

CAR, cellular acute rejection

GEE, General Estimating Equation

QD, once-daily

SD, standard deviation

Clinical study name: ADherence Measurement In stable Renal transplant patients following conversion from Prograft® to ADvagraf® (ADMIRAD)

Clinical trial registration: BE-02-RG-186

Abstract

Background. With effective agents available to prevent post-transplant acute organ rejection, medication adherence becomes a key factor for successful treatment-outcomes after renal transplantation. A once-daily, modified-release oral formulation of tacrolimus has been developed to simplify dosing and improve medication adherence.

Methods. ADMIRAD is a randomized multi-center controlled trial to evaluate adherence between a tacrolimus once-daily(QD) and a tacrolimus twice-daily(BID) regimen using an electronic monitor to document drug intake. After enrolment, all patients continued the BID regimen for 3 months, then were randomized 2:1 between the two formulations and followed for 6 months. Adherence was decomposed into patients' persistence and implementation of each regimen.

Results. 219 patients (45% male; 3$\pm$2 years post-transplant) were analyzed (145 QD, 74 BID). At six months after randomization, 81.5% of the QD and 71.9% of the BID patients remained persistent with the treatment (p=0.0824). Among patients who remained engaged with the regimen, 88.2% of the QD vs. 78.8% of the BID patients (p=0.0009) took the prescribed number of daily doses. When the patients took the BID regimen, the average percentage of missed doses is 11.7% in the morning and 14.2% in the evening (p= 0.0035).

Conclusions. Regimen implementation of tacrolimus QD is significantly superior to the BID regimen. There was a residual prevalence of sub-optimal adherence that will have to be countered by means other than reformulation and regimen simplification. Electronically compiled dosing histories provide detailed data on patient adherence that can be used for efficient medication management.

1. Introduction

With effective agents available to prevent post-transplant acute organ rejection, medication adherence becomes a key factor for successful treatment-outcomes after renal transplantation. Suboptimal adherence to the immunosuppressive regimen causes a higher risk of late acute rejection and allograft loss (1-9). A meta-analysis found that non-adherence to immunosuppressant was highest in renal recipients (10).

Evidence from many fields of ambulatory pharmacotherapy shows that less frequent dosing regimen leads to higher percentage of prescribed doses taken (11,12). A once-daily, modified-release oral dosage form of tacrolimus has been developed to simplify dosing and improve medication adherence in ambulatory post-transplant patients. The safety, efficacy, and tolerability of the modified-release once daily tacrolimus have been described in several studies (13-17). Pharmacokinetic studies have demonstrated that patients can be converted from twice- daily (BID) to once-daily (QD) tacrolimus formulations on a one-to-one total daily-dose basis (18-20).

The primary objective of the ADMIRAD (ADherence Measurement In stable Renal transplant patients following conversion from Prograf® to ADvagraf®) study is to compare medication adherence between modified-release tacrolimus QD and tacrolimus BID regimen. The positive impact of regimen simplification of immunosuppressive drugs to prescribed dose taken has been confirmed in renal transplant recipients (9). The superiority of adherence to tacrolimus QD relative to that of the conventional BID regimen has been suggested in other studies (13, 21) , yet this has not been tested in a randomized controlled trial. ADMIRAD was the first randomized controlled study to compare medication adherence between tacrolimus QD and BID regimen, using electronic monitoring.

Electronically compiled drug dosing histories of treated patients provide richly sampled and reliable objective data on patient adherence to the medication (22). As each dosing time and date are automatically recorded electronically, the collected data provide accurate times of intervals between successive doses, from the first-taken to the last-taken dose.

2. Results

From October 2008 through September 2009, 252 patients were enrolled in the ADMIRAD study at 6 clinical sites across Belgium. After 3 months of baseline adherence evaluation, 219 patients (87%) were randomized: 145 patients were allocated to the QD regimen and 74 patients were allocated to the BID regimen. Of the patients allocated to the QD regimen, 43% of them were female, 11% of them had a second transplantation, and the randomization occurred on average 3.1 (+/- 2.0) years since their last renal transplantation. Of the patients allocated to the BID regimen, 38% of them were female, 11% of them had a second transplantation, and the randomization occurred on average 2.9 (+/- 2.1) years since their last renal transplantation.

Figure 1 describes the study flow diagram. Among the randomized patients, 14 (9.7%) QD patients and 8 (10.8%) BID patients withdrew earlier than the end of the study period. No patient had an acute rejection during the study. The last patient's last visit occurred in July 2010. Different adherence patterns were observed among the patients in this study (Figure 2). From the collected patients' dosing history data, we analyzed adherence to both regimens by distinguishing patients' persistence (how long the patients stayed with the treatment) and implementation (how well the patients implemented the regimen while still engaging to the treatment) of the regimens (23).

2.1. Patients' persistence with the medication

Patients' persistence with the medication, described as the percentage of patients who remained engaged with the regimen over the study period, is shown in Figure 3. Persistence with the regimen was marginally higher in the QD than in the BID group (log-rank test, p=0.0824). At six months after randomization, 81.5% of the QD patients and 71.9% of the BID patients were still engaged with the treatment. At the time of randomization the percentage decrease of the QD and BID group are estimated to be 5.5% and 6.8%. This sudden drop at randomization occurred in both groups

indicating that some patients decided to discontinue participation in the trial, immediately after being allocated to each group.

2.2. Patients' implementation of the dosing regimen

Patient's implementation of the dosing regimen is analyzed by evaluating the day-by-day percentage of patients with correct dosing of each regimen over the study period (Figure 4). The percentage calculation was based on the patients who were still engaged to the treatment (persistent) at the time in question, adjusting for the effect of non-persistence with the regimen. After randomization, implementation was significantly better in the QD compared to the BID group (GEE model, p=0.0009). The estimated difference between the two curves is 9.8% (88.2% QD vs. 78.8% BID). Time (days since randomization) is not a significant variable in the model (p=0.9765). The difference between pre- and post-randomization implementation (82.2% pre vs. 88.2%post) is significant for the QD group (p<0.0001) and not significant for the BID group (79.5% pre vs. 78.8% post, p=0.7871). The proportion of patients having at least one single skipped BID dose/month is 84%. The proportion of patients having at least one day interval without a dose per month (missing a single dose for QD or missing two consecutive doses for BID regimen) is 62% for QD and 40% for BID patients.

The adherence assessment without adjusting for the effect of non-persistence (Figure 1, Supplemental Digital Content) shows that the percentage of patients with correct dosing after randomization was higher in the QD compared to the BID group (GEE model, p=0.0026).

Timing adherence assessment described by day-to-day percentage of patients who dosed consistently within 2 hours of their respective average intake time (Figure 2, Supplemental Digital Content) shows higher percentage of patients who dosed timely after randomization in the QD compared to the BID group (83.7% QD vs. 73.4% BID; GEE model, p=0.0015).

The percentages of missed doses by days of the week and by the time of the day for patients prescribed the BID regimen are described in Figure 5. Saturday's percent of missed doses was

significantly higher than that of the other days (p= 0.0285), while Sunday's percent of missed doses was significantly lower that of the other days (p=0.0276). Saturday evening was the time within the week with most dose omissions (15.6%). The average percentage of missed doses is 11.7% in the morning and 14.2% in the evening (p= 0.0035). The percentage of missed doses was significantly higher ($p<0.05$) in the evening than in the morning for each day of the week, except for Wednesday (p=0.1245).

The average number of dose adjustments after randomization was significantly higher in the QD group than in the BID group (p=0.0092, 1.7 QD vs. 1.0 BID). The average total number of tacrolimus concentration measurements per patient after randomization were marginally higher in the QD than in the BID group (p=0.0901, 3.8 QD vs. 3.4 BID). The difference of the number of concentration measurements between the two groups occurred in the first two weeks after randomization ($p<0.0001$, 0.7 QD vs. 0.3 BID). After two weeks, the number of measurements are equivalent between the two groups (p=0.5743, 3.1 QD vs. 3.1 BID). The average tacrolimus concentrations in the QD and in the BID group were 7.2 ng/l and 8.1 ng/l (p=0.0004) with between-subject standard deviation of 1.8 ng/l and 1.9 ng/l (p=0.8672) (Figure 3, Supplemental Digital Content). The within-subject standard deviation of tacrolimus concentrations in the QD and in the BID group were 2.1 ng/l and 2.5 ng/l (p=0.0911).

3. Discussion

This study has demonstrated superior implementation of the tacrolimus QD regimen to the BID regimen. Improvement of regimen implementation took place after the BID to QD regimen switch, as the burden of the patient to take an additional dose each day was eliminated. Moreover, the regimen simplification eliminates evening doses that pose higher incidence of missed doses relative to morning doses in the BID regimen. An example of a dosing history of a patient who benefits from a regimen switch from the BID to the QD regimen is illustrated in Figure 2(v). Taking evening doses in the BID regimen was a burden for this patient. Patients' morning activities are relatively more

structured than the evening ones, making it easier to associate dose intakes to certain habits or rituals. A similar conclusion has been demonstrated for hypertensive patients treated with a QD regimen; patients who took their dose in the morning have less chance to miss their dose relative to those who took their dose in the evening (24).

Although the proportion of correct dosing for the QD regimen is higher than the one for the BID regimen, the results of this comparison should be cautiously interpreted. It is generally true that a patient prescribed a BID regimen will be more likely to miss a dose than a patient prescribed a QD regimen, as twice as many doses are prescribed every day for the BID than for the QD regimen. However, the frequency of having at least one day interval without dose is higher in the QD than in the BID regimen. It is therefore important to investigate the pharmacological effect of each type of dosing error. If the pharmacological effect from skipping a single BID dose is appreciably less than to that from skipping a single QD dose, then while some patients (e.g. Figure 2(v)) would benefit from a QD dosing, other patients who maintain the frequencies of skipped doses after a conversion from BID to QD dosing might be better served by a BID regimen. The pharmacological comparison based on both patients' adherence and PK/PD characteristics of tacrolimus is beyond the scope of this project and should constitute the basis for further research.

Persistence was higher with the QD regimen, but the difference was not significant. One possible explanation of this slight difference is that the patients in the QD group had more tacrolimus concentration measurements and dose adjustment relative to the patients in the BID group; therefore they had more clinic visits and attention paid to their ongoing implementation of the dosing regimen. This effect is especially prominent early after the randomization. Clinic visit frequency has been shown to have a positive effect on the persistence with treatment (25).

This study has certain limitations. As it was intended primarily to evaluate objectively the adherence to tacrolimus QD and BID regimen, it did not provide any further information on the link between the adherence data and clinical outcomes. In order to do this comparison, a longer follow up with a

greater number of patients would be needed, which was beyond the scope of this project. The study design was chosen to be simple and as close as possible to daily practice, resulting a limited list of patients' demographic characteristics, only the ones relevant to the patients' eligibility criteria. Bias in adherence to the patients' demographic factors was assumed to be minimal in this randomized clinical trial.

This study shows that more dose adjustments were needed shortly after the conversion from BID to QD regimen. Other studies (26-28) confirm the need for dose adjustment of the QD regimen in the short term, to get the effective therapeutic levels. The mean concentration was significantly lower in the QD than in the BID regimen, as reported in other studies (29,30), however the difference was small and was not reflected in acute rejection.

As transplant recipients are often prescribed multiple immunosuppressants and other medications, setting up an optimal combination therapy would require extra attention to the possible clinically relevant drug interactions (31). Intensive monitoring of drug concentrations and adequate dosing responses are not only necessary for either tacrolimus QD or BID, but is necessary for all concomitant drugs that require therapeutic drug monitoring. The choice of immunosuppressive regimen should be adapted to ensure optimal clinical outcome.

Detailed and objective patients' dosing history data were valuable in this study in identifying specific patterns of non-adherence, such as missed evening doses or delayed weekend doses. They have provided insight into how patients can benefit from a regimen simplification. There was, however, a residual prevalence of sub-optimal adherence that will have to be countered by means other than reformulation and regimen simplification. Electronically compiled dosing histories can be used as feedback to the patients on how well they implement their treatment in clinical practice (32). It sets the stage for focused dialogue between healthcare providers and their patients, increasing the quality of the management time spent. Effective medication management, when guided by reliable,

current dosing history data, can enhance daily implementation of, and long persistence with, the prescribed drug dosing regimen (33,34).

4. Materials and Methods

4.1. Study design

ADMIRAD was a randomized, controlled, open-label, multi-center trial, conducted in Belgium with the primary objective of comparing the medication adherence between patients treated with tacrolimus QD and the conventional BID regimen. The study was designed and implemented in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, the local regulatory requirements and the approval of the local medical ethics committee. All patients were provided with a written informed consent document, which each patient signed.

Adult renal transplant patients, treated with tacrolimus BID for at least 3 months before inclusion, were included in this study. The patients had to have had their first or second renal transplantation between 6 months and 6 years prior to the time of inclusion, and to have stable health status at the time they entered the trial.

After enrollment, all patients continued the BID regimen for a further 3 months to collect baseline adherence data (run-in period). Patients collected their prescribed tacrolimus in their usual local pharmacy. During the entire study, patients' medication intakes were electronically monitored using the Helping Hand™ (Bang & Olufsen Medicom, Struer, Denmark) (35). At enrollment, trained staff at the clinical sites provided instructions on how to use the electronic monitor. The electronic monitor recorded the time and the date when the blister was reinserted in the monitor. Only tacrolimus medication intakes were monitored in this study. The rationale to have a 3-month run-in period is also to eliminate the potential modification of adherence behavior due to monitoring.

Patients were asked to come for a clinical visit three months after inclusion. At this visit, the patients were randomized by the investigator or staff at the clinical sites on a 2:1 basis (QD:BID) for another 6-months of follow-up, and thus converted either to the QD regimen or to continue with the original BID regimen. The randomization sequence was computer generated and centrally done with a block of size 3 stratified by the clinical sites. Patients were asked to come for clinical visit 3 months and 6 months after randomization (end of study visit). At each visit, any biopsy-proven or cellular acute rejection (BPAR/CAR) events and trough level measurements were reported. The adherence data stored in the electronic monitors were downloaded at each visit during the study period. During these visits, the patients did not receive any additional information that might have influenced their adherence. The patients, the investigators and their staff had no access to the dosing history data during the study period. The number of dose adjustments between visits was recorded during the period after randomization. In cases of early withdrawal from the study, the time and the reasons of withdrawal were recorded.

4.2. Statistical Analysis

The primary endpoint of this study was a comparison of post-randomization adherence to the QD and BID regimen. The secondary endpoints included comparison between pre- and post-randomization adherence to the regimen for each group, comparison of within-subject variability of tacrolimus concentration, acute rejection rate, and number of dose adaptations between the two groups. Medication adherence was analyzed by examining how long the patients stayed with the treatment (persistence) and how well the patients implemented the regimen while still engaging to the treatment (implementation). If on a given day, the medication was not taken, there can be two reasons: (1) the patient had previously discontinued treatment (non-persistence) or (2) the patient was still engaged with the dosing regimen but neglected to take a dose on that particular day (non-implementation).

Persistence is defined as the time from the first-taken dose to the last-taken dose. The Kaplan-Meier method was used to estimate the percentage of patients who remain engaged with the regimen over time. The log rank test was used to evaluate if there was any significant difference in the persistence between the two regimens.

The implementation of each dosing regimen is assessed by evaluating the day-to-day percentage of patients who dosed at least as prescribed among patients who were still engaged with the treatment. When a patient stopped taking the medication, then from the day of discontinuation onward, this patient was censored in the percentage calculation. Longitudinal logistic models (36) were used to evaluate the implementation of the two dosing regimens. The dependence among observations from a given patient over time is taken into account by General Estimating Equation (GEE) models, with a first order autoregressive covariance structure. The dependent variable is the longitudinal binary variable indicating whether the patient took a given day's prescribed dose, or not. The explanatory variables used were the group indicator, the pre- vs. post-randomization indicator, and the number of days since the start of the monitoring. The interaction between these variables was assessed in the models.

The sample size of the trial was determined based on the longitudinal logistic model to evaluate medication adherence, with a 5% significance level, 80% power and 0.20 intra-cluster correlation. In a previous publication (37), the average daily proportion of correct dosing for BID was estimated to be about 70%. This study was powered to detect a 10% increase in adherence to the simplified QD regimen.

A mixed effects model was used to compare the between- and within-subject variability of the tacrolimus concentrations. All statistical tests were performed two-sided at a 5% level of significance. All randomized patients were included in the analysis on an intention-to-treat basis. When a patient stopped taking the medication or dropped out from the study after randomization, then this patient was considered as non-persistent in the analysis of persistence and included in the analysis of implementation of the regimen up to the day of discontinuation.

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Supplementary Digital Content

SDC, Figure 1:

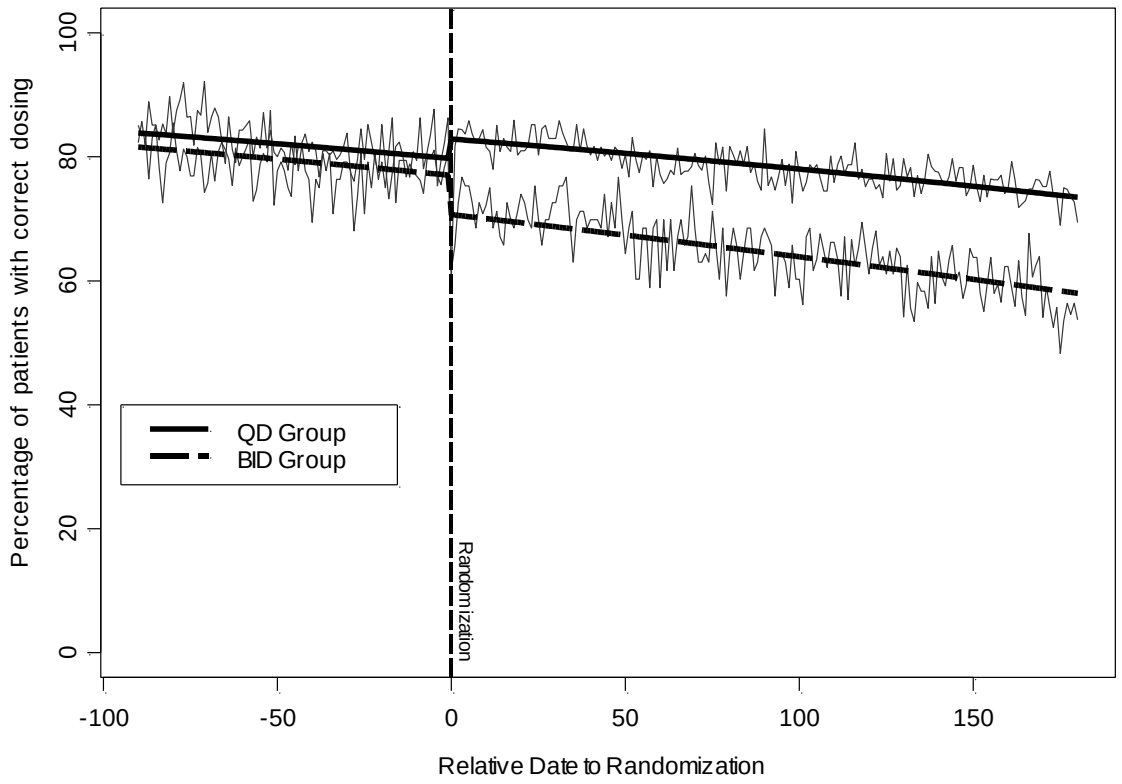

Figure 1. Day-to-day percentage of patients with correct dosing for both groups without distinguishing whether the patient was still engaged with the regimen or not (any missed dose could be caused by either non-persistence or non-implementation of the dosing regimen). Broken vertical line at time 0 represents time of randomization. The overlaying lines are model-based-estimation of the day-to-day percentage of patients with correct dosing for both groups. No difference of overall percentage of correct dosing between the two groups before randomization (GEE model, p=0.4634). After randomization, the percentage of patients with correct dosing was higher in the QD compared to the BID-group (GEE model, p=0.0026). The percentage of patients with correct dosing decreased significantly over time (p<0.0001).

SDC, Figure 2:

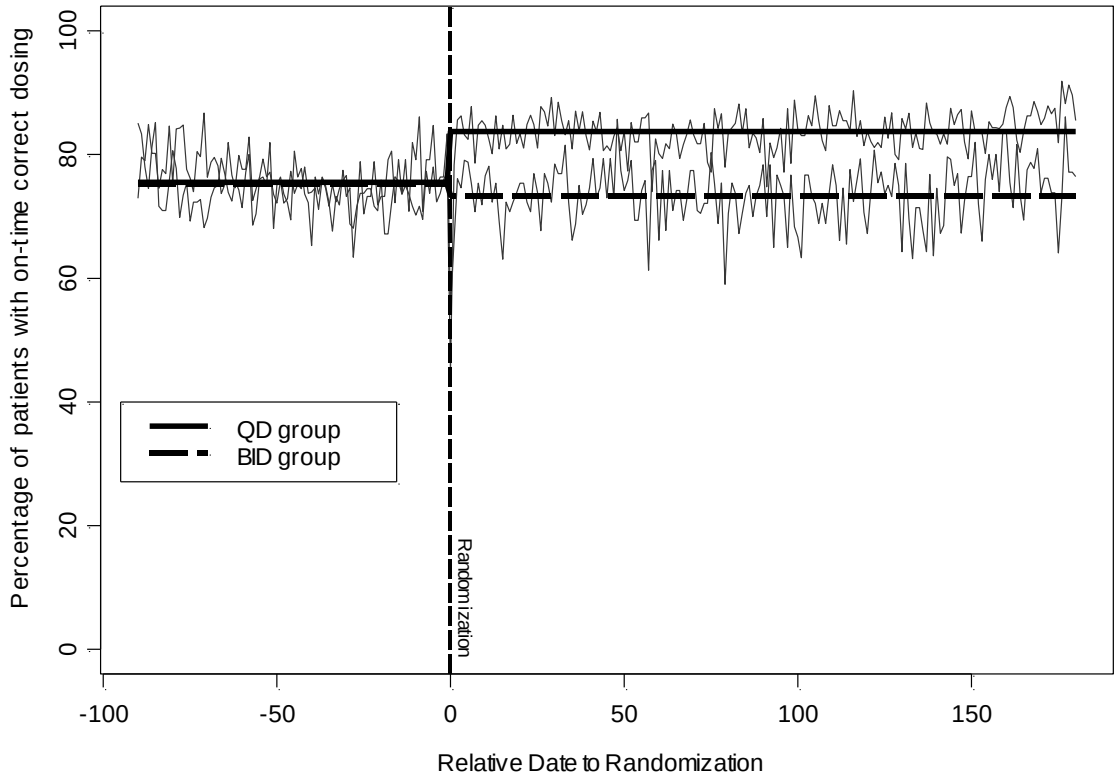

Figure 2. Day-to-day percentage of patients with correct dosing within 2 hours of their respective average time intake relative to patients who were still engaged with the treatment. Broken vertical line at time 0 represents time of randomization. The overlaying lines are model-based-estimation of the day-to-day percentages.

SDC, Figure 3:

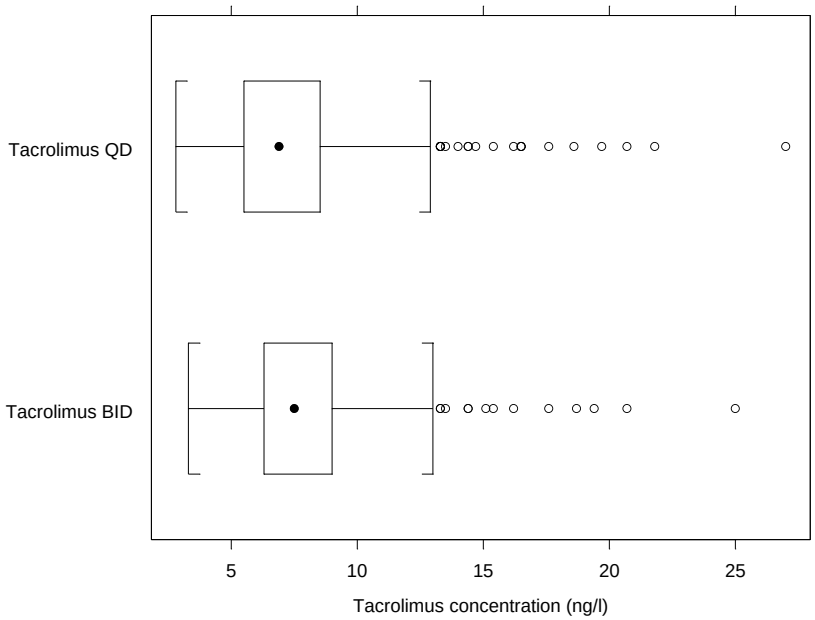

Figure 3. Box whisker plot mean tacrolimus whole blood concentration in both regimens. The point near the middle of the box is the median. The lower and upper bound of the box is the 25th and 75th percentile of the distribution. The ends of the whiskers represent the lowest and the highest values within the 1.5 * the inter quartile range (IQR). The points outside the whiskers are the outliers.

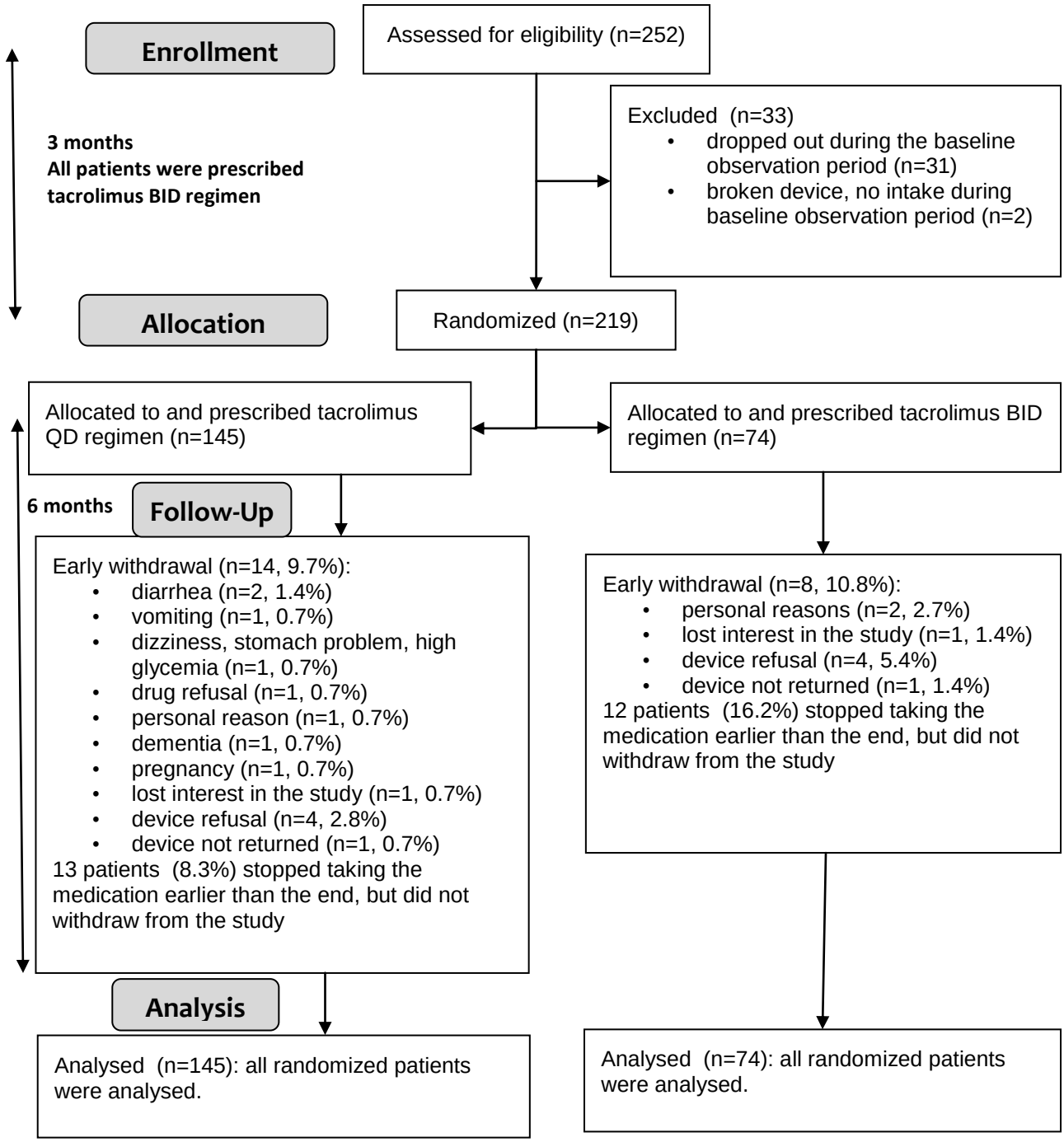

Figure 1. Study flow diagram

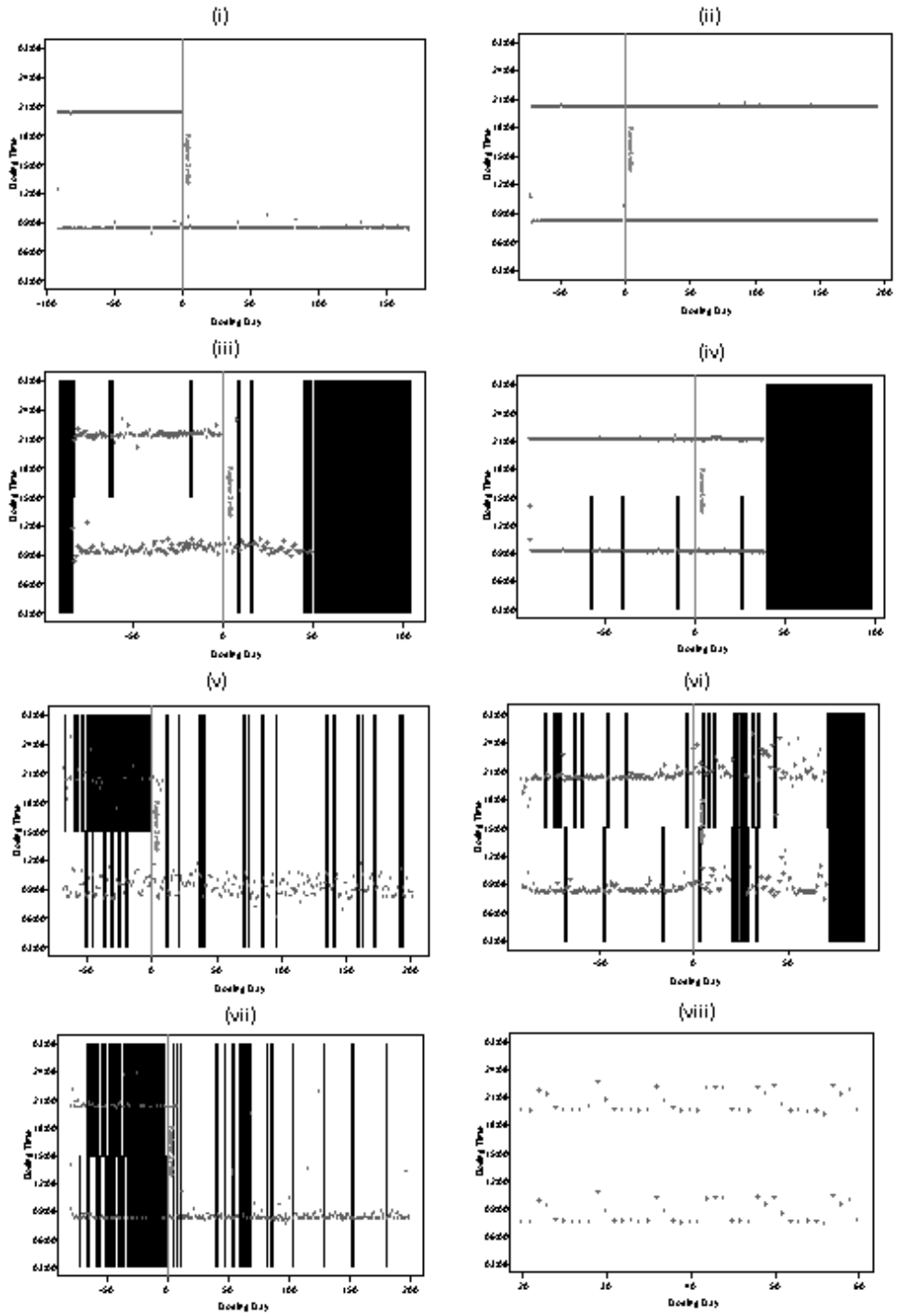

Figure 2. Examples of patient's individual plots of drug intake. The horizontal axis displays the dosing dates relative to randomization (time 0). The vertical axis gives the time of drug intake on a 24-hour clock (Dosing Time) from 3.00 am to 2.59 am. Each point corresponds to a blister removal from the container. The grey bars correspond to the missed doses. Left panels are examples taken from patients with QD regimen after randomization. Right panels are examples taken from patients with BID regimen after randomization. Figure (i) and (ii) are patients with perfect dosing who took their

doses at the same time every day. Figure (iii) and (iv) are patients with short persistence who stop taking the medication earlier than prescribed. Figure (v) and (vii) are patients that had better adherence after regimen switch from BID to QD. Figure (vi) is a patient who had a worsened regimen implementation before quitting the regimen. Figure (viii) is a dosing history snapshot of a patient who took the medication at a later time of the day during weekends.

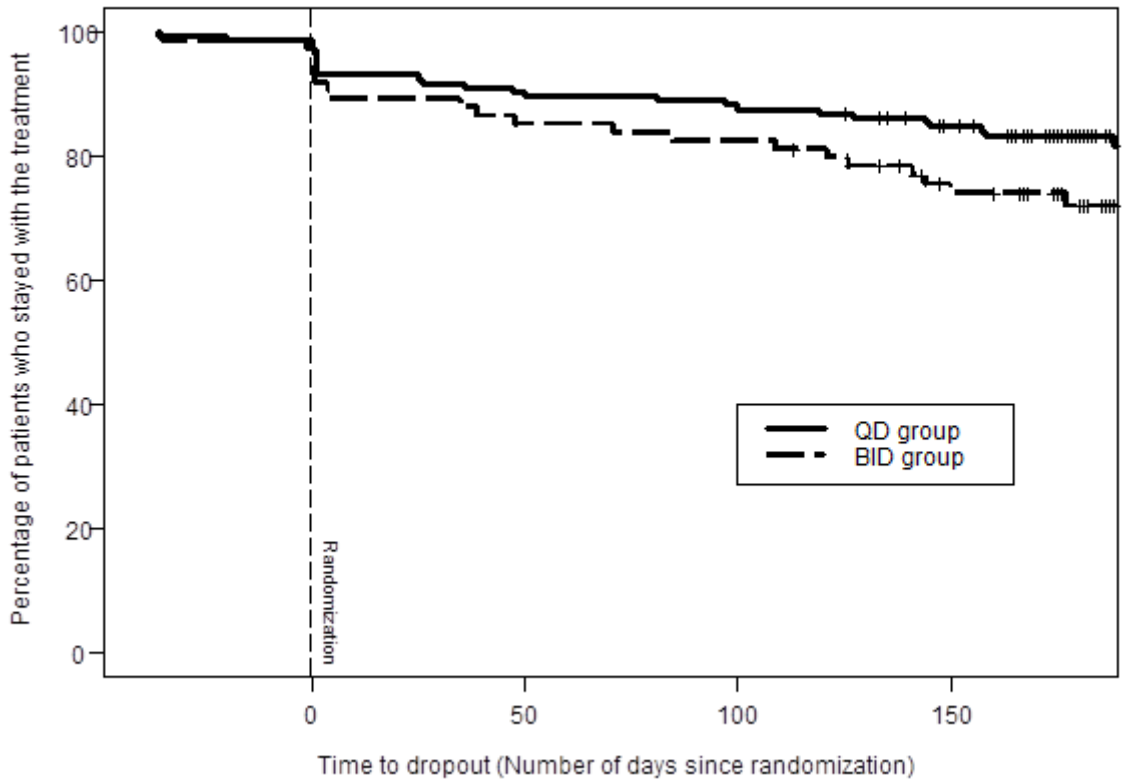

Figure 3. Kaplan Meier estimates of the percentage of patients continuing with the treatment over time. Each small vertical tick-mark indicates that a patient was censored in the calculation as he/she completed the study.

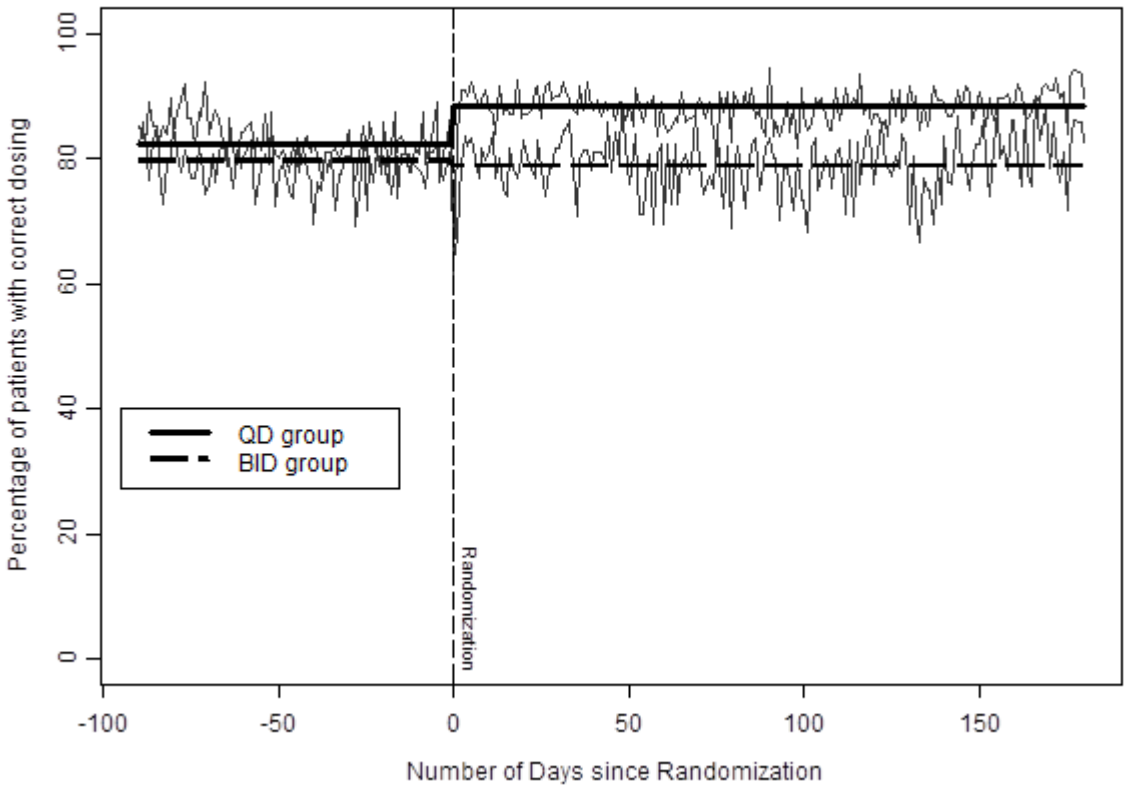

Figure 4. The implementation of each dosing regimen represented by the day-to-day percentage of patients with correct dosing relative to patients who were still engaged with the treatment. Correct dosing is defined when the number of the medication intake that day is at least as prescribed. Broken vertical line at time 0 represents time of randomization. The overlaying lines are model-based-estimation of the day-to-day percentages.

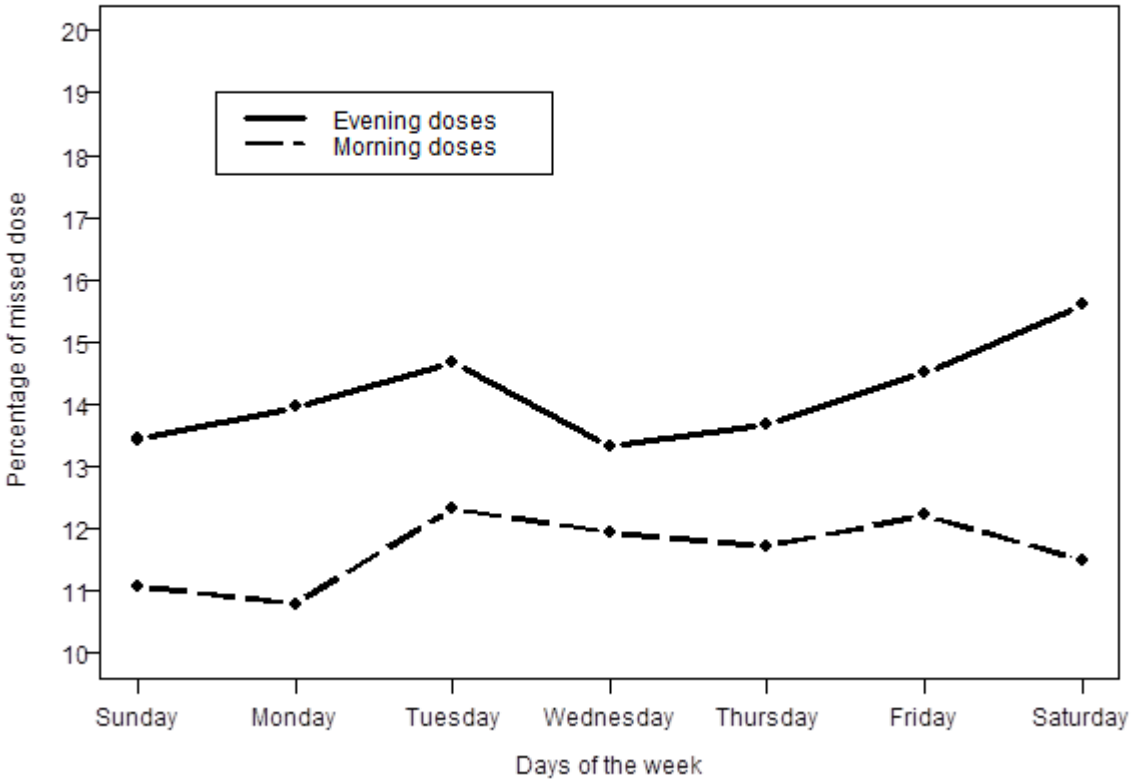

Figure 5. Percentage of missed doses by days of the week and morning/evening doses when the patients were prescribed the BID regimen and were still engaged to the treatment.